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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/038,899	01/08/2002	Kokichi Kikuchi	216432US0XDIV	3573

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EXAMINER	
KAUSHAL, SUMESH	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 01/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/038,899	KIKUCHI ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-20* is/are pending in the application.

4a) Of the above claim(s) *14-18 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 08/723,116.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response filed on 09/02/03 has been acknowledged.

*Applicants are required to follow Amendment Practice under revised 37 CFR §1.121 (http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/revamdtprac.htm). The fax phone numbers for the organization where this application or proceeding is assigned is **703-872-9306**.*

Election/Restrictions

Applicant's election with traverse of Group IV claim 19 in Paper No. 09/02/03 is acknowledged. The traversal is on the ground(s) that invention of Group I and II is Markush group that would not pose a serious burden. The applicant further argues that search of all claims would not constitute a serious burden. This is not found persuasive because a recombinant bacterial vaccine and a recombinant viral vaccine are not so closely related to encompass a proper Markush group. For example a bacterial vaccine may expresses the antigen of interest on bacterial surface, whereas the viral vaccine requires a host cells to the expression of gene of interest. In addition inventions are distinct if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case prevention or treatment of gastric cancer as claimed in groups above requires the use of structurally and functionally distinct products i) recombinant bacteria, ii) recombinant virus, iii) peptide and iv) immune

stimulated CTLS. Making of these products requires different reagents and different protocols. Furthermore the mode of action of each product is distinct from another in vivo. For example polypeptides are biologically active reagents whereas the recombinant virus requires a host cell to express the encoded protein of interest. Recombinant bacterial cells are distinct from CTLS, since making of bacterial cells does not require immune sensitization. Thus these inventions arc distinct and are of separate uses.

The requirement is still deemed proper and is therefore made FINAL.

Claims 14-18 and 20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 09/02/03.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C.120 as follows:

This application filed under former 37 CFR 1.60 lacks the necessary reference to the prior application. A statement reading "This is a Division of Application No. 09/103,808, filed 06/24/1998 now U.S. Pat. No. 6,368,852 which is Division of 08/723,116 filed 09/30/1996 now U.S. Pat. No. 5,837,248." should be entered following

the title of the invention or as the first sentence of the specification. Also, the current status of all nonprovisional parent applications referenced should be included.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 19 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of Invention:

The instant invention relates to a method for preventing or treating gastric cancer by administering into a patient cytotoxic T-lymphocytes (CTL), which has been activated with gastric cancer antigen protein.

Breadth of Claims and Guidance Provided in the Specification:

The scope of the invention as claimed encompasses preventing or treating a gastric cancer by administering CTL, which has been activated with any and all gastric cancer antigen proteins present in a human gastric cancer cell. At best the specification as filed teaches isolation of a polypeptide fragment comprising 10-12 amino acid sequences (SEQ ID NO: 1 and 2) which binds to HLA-A31 and is capable of inducing a

cytotoxic T-cell that targets gastric cancer cells **in-vitro**. The specification as filed fails to disclose all gastric cancer specific peptides that bind to all types of HLA molecule to induce a CTL response against the target gastric cancer cells in-vitro or in-vivo. Furthermore the specification fails to disclose that administration of CTLs activated by any and all peptides (as clamed) would prevent or treat gastric cancer any gastric cancer patient. In addition the specification fails to disclose "what is an effective amount CTL" that would prevent or treat a gastric cancer in a patient. The specification as filed fails to disclose any method that would allow the expansion of a particular tumor specific CTL clone without loosing its specificity.

State of Art and Predictability

The treatment of cancers is considered highly unpredictable because various genetic and etiological factors govern the development of a cancer. Antigens unique to individual tumors not only encompass mutated or rearranged oncogenes, tumor suppressor genes and viral genome encoded proteins but also the over expressed differentiation antigens or embryonic antigens (Shu et al, JAMA 278(22):1972-81, 1997 table 20.1, 20.2, page 1975-76). Down regulation of expression of antigens in cancer cells also represent a problem for the development of immuno-therapies because of the possible immunoselection of non-expressing tumor clones. For this reason an ideal target for the immune destruction is a protein that is essential for the malignant phenotype (Rosenberg, Immunity, 10:281-287, 1999). The state of the art clearly suggests that there is critical need to develop diversity of strategies and more efficient methods for identifying tumor specific antigens (Pardoll et al Curr. Opin. Imm. 10:588-

594, 1998, page 592, col.2 para.3). Despite considerable advances in the understanding of the basic mechanisms underlying immune non responsiveness, the specific cellular immunological mechanisms that tumor cells exploit to avoid CTL mediated rejection is still not very well known (Antonia et al, Crit. Rev. Onc. 9(1):35-41, 1998 page 35, page 38, col.2, para.2). In addition the efficacy of tumor infiltrating lymphocytes is limited because tumor antigen that are targets for the effector cells are not well defined and infused cells have sub-optimal in-vivo survival and function, along with the poor localization of T cells to tumor sites (Yee et al, Curr. Opin. Imm. 9:702-708, 1997). The art at the time of filing concluded that development of cancer immunotherapies based on the molecular characterization of tumor antigens is highly unpredictable and is in its early stages of development. The selection of target antigen or epitope for directing therapy will need to be considered in the light of a number of factors including: i) the prevalence of antigen expression by tumor cells, ii) the feasibility of isolating antigen specific T-cells from patients and iii) potential for the adoptive transferred antigen specific T-cells to induce toxicity in normal tissues (Rosenberg, Immunity 10:281-287, 1999, Yee et al, Curr. Opin. Imm. 9:702-708, 1997).

In addition F4.2 (a gastric cancer antigen) is the only art recognized antigenic peptide found in the human gastric cancer which induces HLA-A31-restricted autologous CTL response in TcHST-2 clonal T-cells (Nabeta et al Jpn. J. Cancer Res. 91;616-621, 2000, see page 620 col.2). The instant specification fails to identify all gastric cancer specific peptides that bind to all kinds of HLA molecule to induce a CTL response against the target gastric cancer cells in-vitro or in-vivo. Furthermore only

16.5% gastric cancer patients are positive for HLA-A31 expression (see Nabeta et al, page 617 col.2). Therefore to elicit a CTL response in the tumor cells lacking HLA-A31 expression one skill in the art would have to genetically modify the HLA-A31 negative tumor cells to express HLA-A31 genes (Suzuki et al J. Immunol. 163:2783-2791, 1999 see page 2783, col.2). In addition expansion of CTL clones to obtain a considerable number of cells is problematic, since the stimulation of CTL with mitogen and/or IL-2 results in loss of cytotoxic of CTLs (Wada et al J. Immunological Methods 154:235-243, 1992. see page 241 col.2). The specification as filed fails to disclose any method that would allow the expansion of a particular tumor specific CTL clone without loosing its specificity.

Thus considering the state of the art and limited amount of guidance provided in the instant specification the invention as claimed is highly unpredictable. In instant case the CTL based cancer prevention or treatment is not considered routine in the art and without sufficient guidance to a specific therapeutic gene the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number **571-272-0769**. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel Ph.D. can be reached on **571-272-0781**. The fax phone numbers for the organization where this application or proceeding is assigned is **703-872-9306**. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

S. Kaushal
Patent examiner

JEFFREY FREDMAN
PRIMARY EXAMINER